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Original Article

Comparative Study of Hypovitaminosis B12 Associated with Metformin in Combination with Sulfonylurea or Dpp-4 Inhibitors

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ABSTRACT

Introduction: The purpose of this study was to estimate the prevalence of hypovitaminosis B12 effect of metformin and its combination with sulfonylureas or DPP-4 inhibitors for type-2 diabetes mellitus patients. Retrospective chart analysis was done for patients seen by a provider between January 1 and December 31, 2019. **Materials and Methods:** The study was conducted at Shadan Teaching hospital and research centre, Peerancheru, Hyderabad, Telangana. The study period was six months which started from September 2022. 150 patients were enrolled in study based on inclusion and exclusion criteria. This data was analysed using ANOVA [one way Analysis] and the results were computed. **Results:** The main result was the frequency of monitoring for vitamin B12 within a year. The prevalence of normal (>350 pg/mL) levels and deficient (200 pg) levels was compared. Correlation of vitamin B12 levels and the parameters such as age, gender, duration of T2DM and diabetic neuropathy was done and represented graphically. Low, Borderline and Normal levels of vitamin B12 were determined with respect to the grades of diabetic neuropathy. **Conclusion:** According to our findings, the patients who are on metformin therapy singly had a greater prevalence of Vitamin B12 deficiency. In comparison to patients receiving Metformin and DPP-4 Inhibitors, those receiving Metformin and Sulfonylureas combination therapy had a comparatively greater rate of Vitamin B12 deficiency. The severity of diabetic neuropathy, a low Vitamin B12 diet, poor medication adherence and hyperglycaemia all contributed to the inference of severe vitamin B12.

Keywords: B12 Deficiency, Diabetic Neuropathy, OHA combinations, Prevalence.

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INTRODUCTION

Chronic metformin use has been linked to vitamin B12 insufficiency, which was initially identified by Berchtold *et al*. in 1969 and has since been supported by several research.[1] Comparing the obtained prevalence of metformin associated Vitamin B12 deficiency from earlier epidemiological studies is not straightforward and should consider several factors. According to the American and European diabetic associations, metformin is a significant medication that is used as a first-line treatment for Type 2 Diabetes Mellitus (T2DM) all over the world. By improving insulin sensitivity in the liver and reducing glucose generation, metformin has an anti-diabetic impact. Side effects of metformin therapy are gastrointestinal upset and rarely lactic acidosis. Another clinically relevant side effect of metformin therapy is vitamin B12 deficiency.[2] Despite having a positive adverse effects profile, metformin is linked to several side effects such lactic acidosis and a lack of Vitamin B12.[3] For effective management of Type 2 Diabetes Mellitus (T2DM), combination therapy, which addresses both insulin resistance and beta-cell dysfunction, is essential. When metformin alone is insufficient, sulfonylureas and DPP-4 Inhibitors are the most accepted second-line add-on to metformin; especially in Indian clinical settings.[4] Sulfonylurea drugs has a rapid onset in reducing blood glucose levels, but the risk of hypoglycaemia and weight gain increases. The new drugs for second-line therapy that have a lower risk of hypoglycaemia and weight gain are DPP-4i drugs such as sitagliptin, vildagliptin and linagliptin.[5]

Between 5 and 40% of metformin using patients have vitamin B12 deficiencies, depending on the demographic. According to a recent study from the National Health and Nutrition Examination Survey (NHANES), vitamin B12 insufficiency was observed in 5.8% of diabetes patients using metformin[6] and 2.4% of diabetic

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patients not using metformin.[1] Although the exact process by which vitamin B12 deficiency develops in people taking chronic metformin is unknown, potential mechanisms include altered small intestinal motility, which leads to bacterial overgrowth and inhibits the absorption of the vitamin B12 intrinsic factor complex.[7]

In a recent investigation, we clearly showed that the daily dose of sulfonylurea in patients with type 2 diabetes induced a significant fall in the mean blood vitamin B12 level and an increase in the prevalence of vitamin B12 deficiency. The individuals with vitamin B12 deficit were shown to be older, consume more sulfonylurea with metformin and have lower levels of HbA1c when compared to those without vitamin B12 deficiency.[8] According to a study by Fahmi Yousef Khan *et al*., co-administration of metformin with dipeptidyl peptidase-4 inhibitors results in a severe shortage of Vitamin B12 levels. Prospective investigations are required to confirm and delve more into the mechanism behind this observation, as the cause for it is not obvious.

According to the American Diabetes Association's proposals, patients taking metformin should undergo routine testing for Vitamin B12 deficiency and combination therapy with Oral Hypoglycaemic Agents (OHAs) is advised given recent research linking Vitamin B12 deficiency to diabetic neuropathy.

Metformin induced vitamin B12 deficiency among patients with T2DM

The risk of developing vitamin B12 deficiency associated with metformin is significantly influenced by increasing age, dose of metformin and duration of use. Evaluation of the relationship between serum B12 concentration and metformin use by the American Diabetes Association, the National Institute of Neurological Disorders and Stroke, or the National Institutes of Health may lead to changes in the use of vitamin B12 supplementation. This is clinically important because patients with diabetes often suffer from neurological symptoms, such as numbness, paraesthesia and impaired vibration sensation and proprioception.[9] Numerous studies have linked metformin and vitamin B12 deficiency in the body. In observational studies, 10 of 17 studies of type 2 diabetes patients on metformin had statistically lower B12 levels ranging from 28 to 48% among long-term patients who continued to use sulfonylurea.

Vitamin B12 deficiency is accompanied by several neurocognitive or hematological manifestations.[10] Axonal demyelination, degeneration and later death are hallmarks of neuronal damage caused by vitamin B12 deficiency, which manifests as severe peripheral or autonomic neuropathy, subacute combined spinal cord degeneration, delirium and dementia.[11] Prescribing information for metformin in the United States includes annual monitoring of hematologic parameters for anemia secondary to a potential for decreased vitamin B12 absorption.[12]

To identify peripheral diabetic neuropathy, use tools like the biothesiometer, monofilament testing and lack of ankle jerk. The fact that the only study done before ours failed to demonstrate an association between Vitamin B12 shortage and diabetic neuropathy, as well as a significant difference in serum VitB12 levels between various anti-diabetic treatment groups.[3,13] Different studies were conducted to investigate the efect of metformin-induced Vitamin B12 defciency to cause or worsen, PN in patients with diabetes.[14]

Vitamin B12 deficiency's effects must be investigated, which would be useful for future health planning to prevent poor outcomes and improve the management of Vitamin B12 deficiency in rural communities. Need for awareness and general knowledge is very essential to improve the patient conditions. There are very few community-based researches on this subject in rural settings. In tertiary care facilities like our hospital, where patients from both the high-risk community and the low-risk group seek medical care, this type of approach is absolutely essential. To find out how common Vitamin B12 deficiency is among diabetic patients. To investigate the relationship between metformin and a lack of Vitamin B12 in order to work on safer combination of OHA.

MATERIALS AND METHODS

The protocol for approval was submitted to the ethics committee of Shadan hospital After receiving the approval, a retrospective study was carried out. Data was collected from the Medical Record Department (MRD) of Shadan institute of medical sciences. The general medicine department provided the necessary information. The data base consisted of routine monitoring figures on vitamin B12 deficiency was acquired throughout 150 patients and was conducted for a period of 6 months. A hospital based, comparative analytical study conducted in Shadan general hospital, during a period of 6 months retrospectively. According to the reference articles, the sample size was determined. 46 instances in each group will be needed as the sample size to confirm the difference in these proportions with a 95% confidence level and an 80-power level. 50 instances total were collected for each group. Accounting for 150 cases all over the study, the cases were divided based on the OHA into groups as singly metformin, metformin+ sulfonylurea and metformin+dpp4 inhibitor. We identified patients diagnosed with DM or prediabetes who were treated with metformin or any other combination for more than 3 months.

Inclusion criteria

Our study sample include Patients with Type-II Diabetes mellitus of age group: 30-80 years. All patients were taking metformin based oral hypoglycaemic agents for at least 3 months or more.[15] We also consider in account the Patient with combination therapy of ADD.

Exclusion criteria

There are certain characteristics which make a subject ineligible to be included in our study such as Patients who are vegetarians and malnourished, Patients who are not willing to participate and Patients with any other comorbidity like cancer, hypothyroidism are also excluded from the study. Exclusion of subjects is also made on the basis of exceptions like alcoholic patients, pregnant women and patients that underwent certain procedures like ileectomy. Patients who are on some medications like calcium or vitamin supplements and any other drug that causes peripheral neuropathy are excluded.

Statistical analysis

All the analysis in this study was performed by using descriptive analysis. we performed 3 pairwise comparisons in a mono therapy and dual combination therapy (met vs met+su vs met+dpp4 inhibitor). All the groups were compared with vitamin b12 levels by using a scatter plot. Data with ANOVA (one way Analysis) were presented as mean±standard deviation. All the statistical analysis was performed using SPSS and Microsoft excel.

RESULTS

The demographics and clinical characteristics of T2DM patients for 3 groups were performed by descriptive analysis. Table 1 shows demographic profile of the patients with type 2 diabetes mellitus.

The study population included patients with age ranging from 18 to 80 years. Mean age was found to be 58.62±12.22, 57.34±11.74 and 50.22±9.17 in the respective study groups (Figure 1). 56%, 46% and 54% of the patients were found to be male, while 44%, 54%, 46% of the patients were female w.r.t study groups (Figure 2). The duration of diabetes in the respective study groups ranged from ≤5 to ≥10 years with the mean of 8.28±6.84, 7.48±5.21, 6.98±4.79 years (Table 1 and Figure 3).

Effect of OHA's on Vitamin B_{12} levels

The groups included in our study i.e., Metformin, Metformin+Sulfonylurea and Metformin+DPP-4 Inhibitors, the corresponding mean B12 levels were found to be 199.47±150.1 pg/mL, 209.88±112.0 pg/mL and 294.42±127.4 pg/mL and the vitamin B12 deficiency was found in 33 (66%), 30 (60%) and 13 (26%) patients respectively. Higher mean vitamin B12 level was found in the patients receiving Metformin+Sulfonylurea combinational drugs (Table 2).

Non-significant dip of vitamin B12 levels in the patients from 38 in the baseline to 3 in the follow-up in metformin study group and almost straight lines of vitamin B12 levels from 38 in the baseline to 25 in the follow-up in metformin+DPP-4 inhibitors were observed (Table 3 and Figure 5).

Correlation between diabetic neuropathy and vitamin B12 deficiency

Of the 150 patients included in this study, it was possible to establish the presence or absence of diabetic neuropathy in patients using clinical history and nerve conduction study. Interestingly, we found a correlation between having lower levels of vitamin B12 and having a positive diagnosis of diabetic neuropathy. Neuropathy was defined and categorized on the basis of grades. Patients with grade I diabetic neuropathy (≤15 Hertz) does not show any clinical symptoms are more in number. Comparatively, patients with grade II diabetic neuropathy (16-25 Hertz) are frequently having low levels of vitamin B12 which is characterised by pain, neuropathic deformity and foot ulcers than patients with grade III diabetic neuropathy (≥25 Hertz) associated with loss of sensation (Table 4).

The above Figure 6 represents the number of patients with normal, borderline and low Vitamin B12 levels with respect to each study group. By perceiving the above graph, we figured out that metformin in combination with Dpp4 inhibitors have maximum patients within the normal limit of vitamin B12. On compliance with the results, metformin in combination with Dpp4 inhibitor was found to be more effective with respect to vitamin b12 levels. Till date there are no guidelines on recommending this combination over any other in T2DM although many recent studies have discussed its efficiency.

Table 1: Mean Values of all Observations.

Characteristics	Metformin	Metformin+Sulphonylureas	Metformin+DPP4
	Mean±SD	Mean±SD	Mean±SD
Number of patients recruited.	50	50	50
Number of patients at follow-up.	50	50	50
Age (years).	58.62±12.22	57.34±11.74	50.22±9.17
Gender (M/F).	Male-56% Female-44%	Male-46% Female-54%	Male-54% Female-46%
Duration of Type 2 Diabetes mellitus.	8.28±6.84	7.48±5.21	6.98±4.79

DISCUSSION

A retrospective chart review was performed at a tertiary care hospital for 150 patients seen by a provider between January 1, 2019 and December 31, 2019.

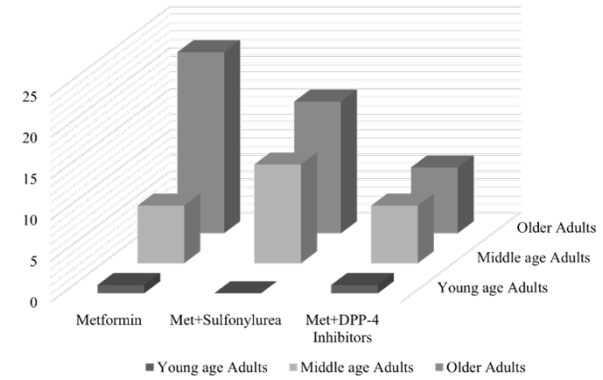

Figure 1: Correlation of vitamin b_{12} levels and age groups.

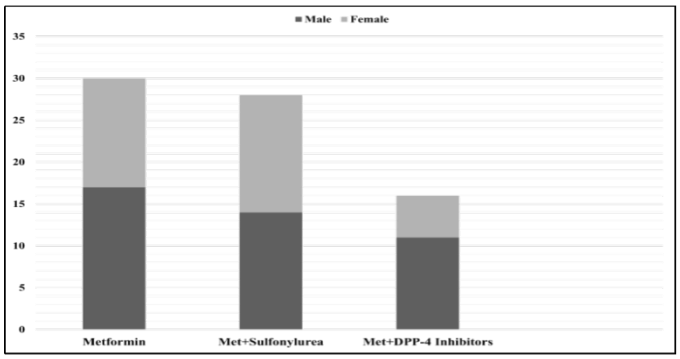

Figure 2: Correlation of vitamin b_{12} levels and gender.

Our study was more significant association between singly used metformin and combination with sulfonylureas and Dpp4 and a higher prevalence of vitamin b12 deficiency in patients with T2DM is determined. This study provides the first analysis of metformin associated vitamin b12 deficiency in response to combined hypoglycaemic medications and also demonstrated its correlation with diabetic neuropathy. This study comprised of 150 type 2 diabetic population, of which the parameters are discussed as follows:

Among the age group of 30-80 years, results of this study are consistent with the findings of P. Agarwal *et al.* In the gender-wise distribution of subjects, 28 were male while 22 were female. The Male: Female ratio was found to be 1.2:1. In contrast, a study of Gillespie km *et al.* reported a male: female ratio of 3:2. Besides age and gender;[16] the duration of DM-II was considered which ranged from 5-10 years, a similar study of Josie MM Evans was noted.[2]

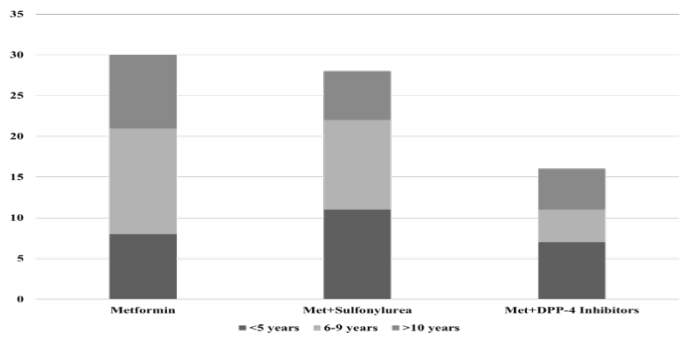

Figure 3: Correlation of vitamin b_{12} levels and duration of T2DM.

Table 2: Characteristics distribution of T2DM patients (*n*=150).

Variable	Category	Vitamin B12 Deficiency					
		Metformin Group (*n*=50)		Sulfonylureas Group (*n*=50)		DPP-4i Group (*n*=50)	
		Total	Deficit (%)	Total	Deficit (%)	Total	Deficit (%)
Age Group	Young Adults (18-35 years)	3	1 (2%)	2	0	2	1 (2%)
	Middle Age Adults (36-55 years)	18	7 (14%)	23	12 (24%)	36	7 (14%)
	Older Adults (>55 years)	29	22 (44%)	25	16 (32%)	12	8 (16%)
Gender	Male	28	17 (34%)	23	14 (28%)	28	11 (22%)
	Female	22	13 (26%)	27	14 (28%)	22	5 (10%)
Duration of T2DM	≤5 years	22	8 (16%)	24	11 (22%)	29	7 (14%)
	6-9 years	16	13 (26%)	15	11 (22%)	12	4 (8%)
	≥10 years	12	9 (18%)	11	6 (12%)	9	5 (10%)
Diabetic Neuropathy	Grade-I	30	14 (28%)	33	18 (36%)	32	12 (24%)
	Grade-II	16	14 (28%)	14	8 (16%)	14	2 (4%)
	Grade-III	3	2 (4%)	3	1 (2%)	4	2 (4%)

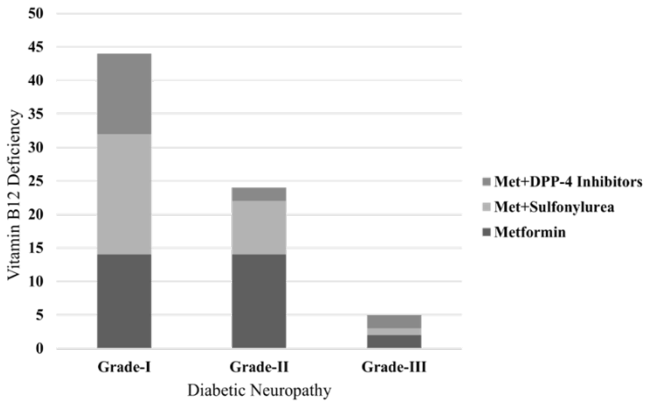

Figure 4: Correlation of serum vitamin b_{12} levels and DN.

A long-standing diabetic duration with long term metformin use may contribute to vitamin B12 deficiency. A study by reddy. *et al.* justified that patient on metformin had a prevalence of vitamin B12 insufficiency about 20.5% and another study by Sun-Hye-ko claimed that 30% of patient receiving metformin has decreased Vitamin B12 levels which can be compared to our study with 66% of greater prevalence. This study also demonstrated that mean blood Vitamin B12 level significantly decreased and the prevalence of Vitamin B12 deficiency increased with daily dosage of sulfonylureas in patients with Type 2 diabetes. Thereby our study validates the contribution of sulfonylureas to the vitamin B12 deficiency.[7,17]

As proved in another study that patients received the metformin and sulfonylurease combination showed higher prevalence of vit b12 deficiency than the patients receiving metformin and insulin where our findings shows that the prevalence of vit B12 deficiency in met+su group is lower than the metformin group. However, several reports including ours, observed that Co-administration of metformin with DPP 4 inhibitor shows significant decrease in vit B12 levels as a study by Fehmi Yusuf Khan shows 34% patients with deficiency which coincide with our results i.e. about 36%. Classically, patients with metformin induced vit B12 deficiency also exhibit some neurological symptoms, such as paraesthesia, impaired vibration sensation and proprioception, which are potential results of neurological damage.[3,18]

A previous study reported an association between low vitamin B12 levels and poor nerve conduction. Neuropathy is an important long-term sequel to diabetes mellitus. Shera *et al* observed that the prevalence of neuropathy in type 2 diabetes is 39.6% in Pakistani patients. Another study by Nazeefa Javed showed about 79% patients had evidence of sensory neuropathy of grade I or II when assessed by biothesiometer. Biothesiometer is a device which can quantify and pick early cases of diabetic peripheral neuropathy. Similarly, our results show that the majority of patients (60-80%) in each group fall in grade I or II diabetic neuropathy according to the biothesiometer values (Table 5 and Figure 4). The biothesiometer can detect sensory neuropathy even if the patients do not have any symptoms of

Table 3: Mean Values of Vitamin B12 in Study Groups.

Parameters	Mean±SD			*p* value
	Metformin Group (*n*=50)	Sulfonylureas Group (*n*=50)	DPP-4i Group (*n*=50)	
Vitamin B12 (Baseline)	486.88±200.0	561.64±180.3	504.62±198.6	0.001*
Vitamin B12 (Follow Up)	199.47±150.1	209.88±112.0	294.42±127.4	

Table 4: Neuropathic grade-specific symptoms of DN.

Neuropathic Grade	Symptoms
Grade-I (up to 15 volts)	No clinical Symptoms.
Grade-II (16-25 volts)	Chronic and Acute pain, Foot ulcers, Neuropathic deformity.
Grade-III (>25 volts)	Loss of sensation.

Table 5: Diabetic Neuropathy according to vitamin B12 levels.

Vitamin B12 level	Diabetic Neuropathy		
	Grade-I	Grade-II	Grade-III
Low	41 (27%)	23 (15%)	7 (5%)
Borderline	18 (12%)	5 (3%)	2 (1%)
Normal	34 (22%)	16 (11%)	1 (0.6%)

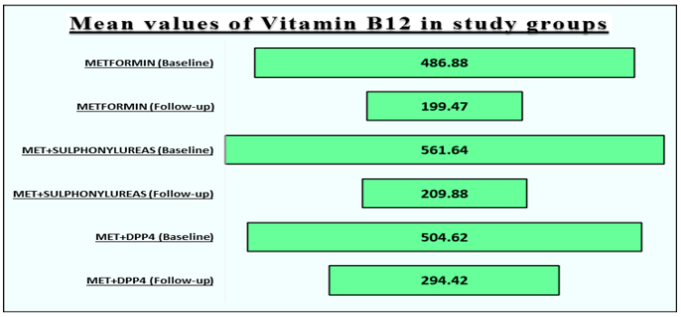

Figure 5: Mean values of Vitamin B12 in study groups.

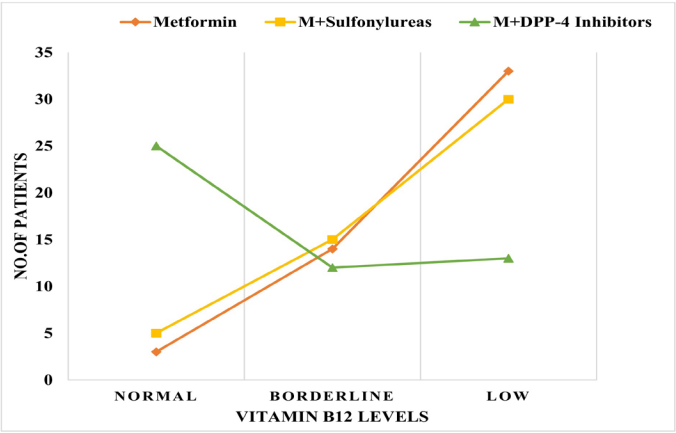

Figure 6: Relationship between serum vitamin B12 and OHA'S

neuropathy. Accordingly, in a study by sun Hye ko 21.8% of patient had typical diabetic neuropathic symptoms. Our findings concur with these results that we did not find a significant association between vitamin b12 deficiency and diabetic neuropathy but Metformin induced vitamin b12 deficiency had a higher risk of worsening diabetic neuropathy which is unnoticed in major diabetic population.[17,19,20]

Limitations

There are few limitations of this study:

•Dosage regimen of all the patients may vary, which may lead to increased risk in a study.

•Diabetic patients with other comorbidities also result in varying Vitamin B12 levels.

•Our study's primary limitation is that it was a cross-sectional and we did not discover any proof of a temporal association between exposure and result. Patients who took vitamin B12 supplements were not included in the study, which would have made our therapy recommendations more accurate.

•Another limitation of our study is the lack of information on metformin compliance. Both the reaction to metformin and the levels of vitamin B12 might be impacted by compliance.

CONCLUSION

When a study on age-wise distribution of patients involved in diabetes mellitus was conducted, a substantial number of DM-II patients were belonging to the age group of 41-60 years in Metformin study group; 41-50 years and 60-70 years in Metformin and Sulfonylureas study group; and 41-50 years in Metformin and DPP-4 Inhibitors study group (Figure 1).

When a study on gender-wise distribution of patients associated with diabetes mellitus was conducted, it was observed that the majority of the subjects were males in the Metformin study group, females in Metformin and Sulfonylureas study group, whereas males in Metformin and DPP-4 Inhibitors study group (Figure 2).

When a study on duration of Diabetes Mellitus in the diabetic population was conducted, it was found that majority of the subjects i.e., in the Metformin study group 58% of the patients had DM-II for >10 years; 50% of the patients had DM-II for <5 years and >10 years in Metformin and Sulphonylureas study group; and 60% of the patients had DM-II for <5 years in Metformin and DPP-4 Inhibitors study group (Figure 3).

According to our findings, the patients who are on metformin therapy singly had a greater prevalence of Vitamin B12 deficiency but had no knowledge about the outcomes of Hypovitaminosis B12. Metformin in combination with Sulfonylureas and in combination with DPP-4 Inhibitors is the most commonly used combination of OHA's for diabetic population. Patients on combination therapy of Metformin and Sulfonylureas were having relatively higher Vitamin B12 deficiency in comparison with patients who are on combination therapy of Metformin and DPP-4 Inhibitors.

The inference for grievous Vitamin B12 deficiency in patients was caused by a lack of understanding of Vitamin B12 associated symptoms, Severity of Diabetic Neuropathy, a low Vitamin B12 diet, improper medication adherence, hyperglycaemia. A Clinical Pharmacist can assess risk factors early on, improving the patient's quality of life and lowering the incidence of complications of diabetes mellitus. Continuous health education, patient counselling and information about medication adherence and satisfaction at each follow-up is essential to avoid the complications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **DN:** Diabetic Nephropathy; **ADD:** Anti-diabetic Drug; **OHA:** Oral Hypoglycaemic Agents.

ETHICAL APPROVAL

The study was approved by the institutional ethics committee.

SUMMARY

Metformin, on a long-term use considering factors such as age, diet and duration can cause deficiency of vitamin B12 in a patient. If the deficiency persists, it can worsen the nerve damage i.e. diabetic neuropathy. To avoid such conditions, the patients receiving metformin or it's combinations from a longer duration of time should undergo serum B12 test to monitor their vitamin B12 levels. Accordingly, the prescribers should also provide the patient with a safer OHA combination.

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